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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	PETITOU, et al
Serial No.	:	115,593
Filed	:	October 26, 1987
For	:	PROCESS FOR THE ORGANIC SYNTHESIS OF OLIGOSACCHARIDES AND DERIVATIVES THEREOF
Art Unit	:	123
Examiner	:	J. Rollins

New York, New York
February 12, 1988

Hon. Commissioner of
Patents and Trademarks
Washington, D.C. 202314.

INFORMATION DISCLOSURE STATEMENT

Sir:

Applicants hereby submit patents and publications which they believe may be relevant to the examination of this application. This Information Disclosure Statement is accompanied by a Search Report for counterpart application EPO 84999.

A list of patents and publications is set forth on the attached Form PTO-1449 (modified). A copy of each item listed on PTO 1449 is attached.

No English translation was readily available to applicant of Klemer and Kraska. We are informed by our foreign agent that EPO 64012 is a counterpart to U.S. Patent 4,607,025 (cited in this application).

Applicants wish to bring to the attention of the examiner the fact that the instant application is one of four pending applications which relate to the synthesis of oligosaccharides and new oligosaccharides formed thereby. The three other applications are:

Ser. No.	Title	Filing Date
856,855	Method For Carrying Out The Organic Synthesis of Oligosaccharides Containing Galactosamine And Uronic Acid Patterns, New Oligosaccharides Obtained And Biological Applications And Derivatives Thereof	April 14, 1986
734,445	Novel Oligosaccharides, Their Preparation By Organic Synthesis And Their Biological Application.	May 15, 1985
888,527	New Disaccharides Formed By Patterns Having A Glucosamine And Uronic Acid Structure, Preparation Thereof And Biological Applications.	July 21, 1986, continuation of application Ser. No. 451,615,

filed Dec. 20, 1982, which issued as Patent No. 4,607,025 on Aug. 19, 1986.

Concise Explanation of Listed Items:

1. Paulsen was cited in application Ser. No. 451,615 (listed above). Ser. No. 451,615 relates to synthesis of certain heparinic disaccharides. The examiner in that case rejected process claims as obvious over Paulsen, stating that Paulsen showed the preparation of an alpha disaccharide in the same manner as claimed in that case. Paulsen does not disclose the formation of a 1-4 alpha linkage between D-glucosamine and D-glucuronic acid or a 1-4 alpha linkage between L-iduronic acid and D-glucosamine, as claimed by applicants (and as found in heparin). Nor does Paulsen show selective positioning of sulfate groups, as claimed by applicants.

2. Schaub et al., '387, was cited in U.S. application Ser. No. 734,445. Ser. No. 734,445 claims a process for synthesizing certain heparinic tetrasaccharides. At col. 8, Schaub et al. discloses removal of acetyl groups from a saccharide, and formation of a sulfate salt. Schaub '387, however, does not disclose selective positioning of sulfate groups, as claimed by applicants in the present application.

3. Feiser et al., was cited by the examiner in U.S. application Ser. No. 734,445, who stated it discloses conversion of an azido group to an amino group, and acetylation of an amino group.

4. Turvey and Williams discloses, at paragraph 2 page 2119, that a low yield was obtained in attempting to remove benzyl groups in the presence of sulfate groups. A copy of this article was submitted with applicants' supplemental amendment dated 3/6/87 in parent application, Ser. No. 457,931.

The remaining patents and publications were all cited in the attached EPO search report for EPO 84999.

More Relevant References:

5. Sinay, 1978, at p. 1437, discloses the use of imidates in alpha glycoside synthesis.

6. Manthorpe and Gigg disclose, at p. 307, the use, generally, of allyl ethers as protecting groups in galactopyranoside synthesis.

7. Kiss and Wyss, 1972, at p. 3056, report an attempt to prepare heparin saccharide derivatives. A protected D-glucuronic acid is linked to a protected D-glucosamine to form a 1-4 alpha linkage. Applicants claim formation of a 1-4 beta linkage between D-glucuronic acid and D-glucosamine.

8. Wyss et al., 1975, at p. 1847 discloses synthesis of heparin saccharide derivatives having a 1-4 alpha linkage, as in Kiss and Wyss above.

9. Klemer and Kraska, at page 431, discloses the synthesis of a 1-4 beta linkage between D-glucuronic acid and a D-glucosamine. It does not disclose selective positioning of sulfate groups.

Less Relevant References:

10. EPO 64012, Petitou et al., is the equivalent of U.S. application Ser. No. 451,615, now U.S. Patent 4,607,025 which Ser. No. 457,931 is a continuation in part of.

11. EPO 027089, Choay et al., is the European Patent equivalent of Lormeau '662, '758, and '770, which patents were cited by the examiner in the Office Action of June 25, 1986.

The following all disclose heparin chains contained in mixtures:

12. EPO 48231, Lindahl et al., at p. 2 second paragraph, discloses sulfated oligosaccharides which are preferably derived from heparin. Lindahl states these oligosaccharides may "possibly" be synthesized but only discloses obtaining them from natural heparin.

13. Barker et al., discloses at p. 1803, summary, the ability of certain moulds to synthesize an O-beta (2-acetamido-2-deoxy-D-glucosyl) -O- glucuronic acid.

14. Klein and Figura discloses, at p. 249, tetrasaccharides and trisaccharides obtained by treating natural heparin.

15. EPO 14184, Lindahl et al., at p. 3 last paragraph,

discloses heparin fragments having 14-18 sugar units prepared from natural heparin.

16. Ogamo et al., at p. 69, discloses fluorescent chondroitin 6-sulfate and heparin prepared by degradation of natural tissues.

17. Ayotte et al., at p. 297, discloses, fractionation of heparin and heparin sulfate.

18. Kosakai and Yosigawa, at p. 296, discloses, porcine and whale heparins, and sulfated oligosaccharides prepared from heparins, which were coupled with a fluorescent compound.

19. Hopwood and Elliott, at p. 241 and 242 discloses, treating heparins to obtain tetrasaccharides and disaccharides.

20. Seno and Murakami, at p. 190, discloses, digestion products of chondroitin sulfate.

Conclusion:

None of the references teach or suggest a process for synthesizing a protected heparinic condensation product which has protecting groups thereon which allows selective positioning of sulfate groups, as claimed. Nor do any of the references disclose a process for synthesizing a protected heparinic condensation product which has protecting groups thereon which allow selective positioning of sulfate groups, and which may be elongated. Nor do any of the references teach or suggest a process for selecting

positioning sulfate groups on protected heparinic condensation product, as claimed. Nor do any of the references teach or suggest substantially pure heparinic oligosaccharides of a single structure, as claimed.

Respectfully submitted,

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